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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellants: Jane C. Hirsh, Kamal K. Midha, and Whe-Yong Lo

Serial No.: 09/858,016

Art Unit: 1616

Filed: May 15, 2001

Examiner: Sharmilas Gollamudi

For: *PHARMACEUTICAL COMPOSITION FOR BOTH INTRAORAL AND
ORAL ADMINISTRATION*Assistant Commissioner for Patents
Washington, D.C. 20231

APPEAL BRIEF

Sir:

This is an appeal from the final rejection of claims 33-57 in the Office Action mailed July 21, 2003, in the above-identified patent application. A Notice of Appeal was mailed on May 24, 2004. The original Appeal Brief was mailed on July 23, 2004, with an amendment. The Commissioner was authorized to charge \$165.00 for the filing of this Appeal Brief, which is the appropriate fees for a small entity, to Deposit Order Account No. 50-3129. This Brief is filed in response to the Advisory Action mailed October 7, 2004, and the Notice of Non-Compliant Appeal Brief mailed October 7, 2004. It is believed that no additional fee is required with this submission. However, should an additional fee be required, the Commissioner is hereby authorized to charge the fee to Deposit Account No. 50-3129.

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(1) REAL PARTY IN INTEREST

The real party in interest of this application is the assignee Collegium Pharmaceuticals, Providence, RI.

(2) RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences known to appellant, the undersigned, or appellant's assignee which directly affects, which would be directly affected by, or which would have a bearing on the Board's decision in this appeal.

(3) STATUS OF CLAIMS ON APPEAL

Claims 33-57 are pending and on appeal.

(4) STATUS OF AMENDMENTS

The claims were last amended in the amendment mailed on December 3, 2003. Appendix I sets forth the claims on appeal. An amendment accompanies this response. The Advisory Action mailed October 7, 2004, notes that this amendment would be entered.

(5) SUMMARY OF THE INVENTION

The invention is a two component drug formulation. The first component is designed to rapidly release drug within the mouth, where it is taken up in an effective amount through the buccal or sublingual surface. Suitable drugs are low molecular weight compounds (typically under 350 daltons, see page 6, lines 13-15) or the specifically listed compounds (pages 9-10) that demonstrate rapid onset when administered intraorally (page 7, lines 20-23) since they are not ingested, but are absorbed directly into the systemic circulation. These drugs may also have a low bioavailability if administered orally due to first-pass metabolism (page 6, lines 15-19).

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The dosage of the drug is low, in the range of 1 microgram to 50 mg, more typically 10 micrograms to 30 mg (page 6, lines 1-2). The second component is designed to be released orally, where it is swallowed for uptake within the gastrointestinal tract. The first intraoral component is released rapidly, in some cases within 10 minutes of contacting the saliva (page 20, lines 1-2). The release of the second component may be immediate, continuously released, or released after a delay over a period of 0.5 to 12 hours (page 8, lines 1-4). The formulation may be chewable (page 8, line 5). The formulation may contain a signaling system between the first and second component (page 15, lines 5-10). The first and second components may consist of a single layer or multiple layers or a core in a tablet or capsule (page 21). These may be coated with a film or a compression coating (page 21, lines 22-25). The composition may include an effervescent agent (page 22, lines 15-17; page 23, lines 1-3). The second oral component may include a delayed release coating (page 24, lines 24-26) or a sustained release formulation (page 26, lines 24-26) releasing for 0.5 to 24 hours (page 27, line 1).

(6) ISSUES ON APPEAL

The issues presented on appeal are:

- (a) whether claim 51 is indefinite under 35 U.S.C. 112; and
- (b) whether claims 33-43, 45, 47, and 49-57 are obvious under 35 U.S.C. 103 over U.S. Patent No. 5,053,032 to Barclay, et al.;
- (c) whether claims 33-43, 45, and 47-57 are obvious under 35 U.S.C. 103 over U.S. Patent No. 5,702,723 to Griffin in view of U.S. Patent No. 4,661,492 to Lewis, et al.;

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(d) whether claims 44 and 46 are obvious under 35 U.S.C. 103 over U.S. Patent No. 5,702,723 in view of U.S. Patent No. 4,814,181 to Jordan, et al.; and

(e) whether claims 33-39, 42-50, 52, 53, and 55-57 are obvious under 35 U.S.C. 103 over GB 800,973 in view of U.S. Patent No. 4,661,492 to Lewis, et al.

Appellants have agreed to filing of a Terminal Disclaimer in response to the double patenting rejections, once the claims have been found to otherwise be allowable.

(7) GROUPING OF THE CLAIMS

The claims do not stand or fall together as discussed below.

(8) ARGUMENTS

(a) Rejection under 35 U.S.C. 112, second paragraph

Claim 51 has been rejected on the basis that it is drawn to broad drug categories (""), but that it depends from a claim drawn to specific drugs, claim 41.

Claim 41 defines the following composition:

A pharmaceutical composition comprising:

(a) a first intraoral portion which rapidly dissolves or disintegrates intraorally to release a therapeutically effective amount of at least one pharmaceutically active ingredient which is absorbed sublingually in a therapeutically effective level,

the active ingredient having a molecular weight not exceeding 350 daltons or an active ingredient selected from the group consisting of Buprenorphine, Parecoxib, Aceclofenac, Buspirone, Ipsapirone, Fexofenadine, Loratadine, Dexbrompheniramine, Temelastine, Verapamil, Amlodipine, Ergotamine Tartrate, Dihydroergotamine, Ondansetron, Prochlorperazine, Sildenafil, Alprostadil, Sufentanil, Lofentanil, Carfentanil, Nalbuphine, Droperidol, and Haloperidol, being present in an

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amount between 1 micrograms and 50 mg, and having a rapid onset following intraoral administration, and

the first intraoral portion comprising a pharmaceutically acceptable effervescent agent which generates effervescence when contacted with salivary fluid; and

(b) a second oral portion located within the first portion which is released into the gastrointestinal tract in a therapeutically effective amount after the intraoral portion has disintegrated or dissolved. (emphasis added)

Claim 51 therefore further limits the definition of the compounds having a molecular weight not exceeding 350 daltons, which are not limited to specific compounds.

The Advisory Action mailed October 7, 2004, does not indicate whether the amendment to claim 51, now entered, moots this rejection, however, it should have done so.

(b) Rejections Under 35 U.S.C. § 103

The U.S. Patent and Trademark Office has the burden under 35 U.S.C. § 103 to establish a *prima facie* case of obviousness. *In re Warner et al.*, 379 F.2d 1011, 154 U.S.P.Q. 173, 177 (C.C.P.A. 1967), *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598-99 (Fed. Cir. 1988). In rejecting a claim under 35 U.S.C. § 103, the Examiner must establish a *prima facie* case that: (i) the prior art suggests the claimed invention; and (ii) the prior art indicates that the invention would have a reasonable likelihood of success. *In re Dow Chemical Company*, 837 F.2d 469, 5 U.S.P.Q.2d 1529 (Fed. Cir. 1988).

The prior art must provide one of ordinary skill in the art with the motivation to make the proposed modifications needed to arrive at the claimed invention. *In re Geiger*,

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815 F.2d 686, 2 U.S.P.Q.2d 1276 (Fed. Cir. 1987); *In re Lahu and Foulletier*, 747 F.2d 703, 705, 223 U.S.P.Q. 1257, 1258 (Fed. Cir. 1984). Claims for an invention are not *prima facie* obvious if the primary references do not suggest all elements of the claimed invention and the prior art does not suggest the modifications that would bring the primary references into conformity with the application claims. *In re Fritch*, 23 U.S.P.Q.2d, 1780 (Fed. Cir. 1992). *In re Laskowski*, 871 F.2d 115 (Fed. Cir. 1989). The Court of Appeals for the Federal Circuit warned that "the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for showing of the teaching or motivation to combine prior art references." *In re Dembiczak*, 175 F.3d 994 at 999 (Fed. Cir. 1999). The "question is whether there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination. *WMS Gaming, Inc. v International Game Technology*, 184 F.3d 1339 at 1355 (Fed. Cir. 1999). "[T]he showing must be clear and particular." *In re Dembiczak*, 175 F.3d 994 at 999 (Fed. Cir. 1999). Although with the answer in hand, the "solution" now appears obvious, that is not the test. The references must themselves lead those in the art to what is claimed. And in this case, there is simply no such teaching.

1. *The claimed subject matter*

There are two independent claims:

Claim 33, which defines a composition having two components:

(a) a first intraoral portion which rapidly dissolves or disintegrates intraorally to release a therapeutically effective amount of at least one pharmaceutically active ingredient which is absorbed sublingually in a therapeutically effective level,

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the active ingredient selected from the group consisting of Buprenorphine, Parecoxib, Aceclofenac, Buspirone, Ipsapirone, Fexofenadine, Loratadine, Dexbrompheniramine, Temelastine, Verapamil, Amlodipine, Ergotamine Tartrate, Dihydroergotamine, Ondansetron, Prochlorperazine, Sildenafil, Alprostadil, Sufentanil, Lofentanil, Carfentanil, Nalbuphine, Droperidol, and Haloperidol, being present in an amount between 1 micrograms and 50 mg, which is absorbed intralingually in an effective amount and has a rapid onset following intraoral administration; and

(b) a second oral portion located within the first portion which is released into the gastrointestinal tract in a therapeutically effective amount after the intraoral portion has disintegrated or dissolved, wherein the second portion is either a sustained release or chewable formulation.

This composition is limited to specifically named drugs, which are rapidly released sublingually, in an amount between one and 50 milligrams, which have a rapid onset following intraoral administration, in a first oral portion, and includes a second portion that must be in a sustained release or chewable formulation.

Claim 52 defines the active ingredient in the first intraoral composition as having a lower bioavailability upon oral administration when compared to intravenous administration.

Claim 53 further limits the amount of active ingredient in the first intraoral composition to a dosage of between 10 micrograms and 30 mg.

Claim 34 limits the specific compounds of the pharmaceutical composition of claim 33 wherein the active ingredient of the intraoral component undergoes first pass metabolism.

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Claim 37 further limits unit dosage form to a multi-layer tablet wherein the second oral portion of the composition comprises one or more inner layers of the tablet and the first intraoral component comprises one or more of the outer layers of the multi-layer tablet.

Dependent claims 43-46 further limit the composition wherein the second oral component is in a sustained release formulation, wherein the sustained release is over a period of 0.5 to 24 hours, and the composition wherein the composition comprises a delayed release coating, and wherein release is delayed for a period of 0.5 to 12 hours, respectively.

Claims 48 and 49 further specify that the first intraoral component disintegrates or dissolves within 10 minutes, when the composition is contacted with saliva during intraoral administration, and the second oral component remains intact until the intraoral administration of the first intraoral component has been delivered, respectively.

Claim 41 also defines a two component formulation,

A pharmaceutical composition comprising:

(a) a first intraoral portion which rapidly dissolves or disintegrates intraorally to release a therapeutically effective amount of at least one pharmaceutically active ingredient which is absorbed sublingually in a therapeutically effective level,

the active ingredient having a molecular weight not exceeding 350 daltons or an active ingredient selected from the group consisting of Buprenorphine, Parecoxib, Accoclofenac, Buspirone, Ipsapirone, Fexofenadine, Loratadine, Dexbrompheniramine, Temelastine, Verapamil, Amlodipine, Ergotamine Tartrate, Dihydroergotamine, Ondansetron, Prochlorperazine, Sildenafil, Alprostadil, Sufentanil, Lofentanil,

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Carfentanil, Nalbuphine, Droperidol, and Haloperidol, being present in an amount between 1 micrograms and 50 mg, and having a rapid onset following intraoral administration, and

the first intraoral portion comprising a pharmaceutically acceptable effervescent agent which generates effervescence when contacted with salivary fluid; and

(b) a second oral portion located within the first portion which is released into the gastrointestinal tract in a therapeutically effective amount after the intraoral portion has disintegrated or dissolved.

Claim 41 broadens the class of drugs to be administered by including any drugs having a molecular weight of less than 350 as well as the specifically named drugs, but further requires a pharmaceutically acceptable effervescent agent in the first oral portion, which is not required by the other group of claims discussed above.

None of the prior art recognizes the importance of a two component drug, which effectively delivers a first drug (limited to those which can be delivered sublingually in an effective dosage) followed by a formulation of the same or a different drug which is swallowed and released for uptake at a significantly later time.

2. *Rejection of claims 33-43, 45, 47, and 49-57 as obvious under 35 U.S.C. 103 over U.S. Patent No. 5,053,032 to Barclay, et al.*

Barclay

Barclay does not disclose the drugs that are claimed, as the examiner has correctly noted. Barclay does not disclose a first component for sublingual administration, only buccal.

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The examiner refers to col. 12, line 23, as disclosing the claimed amount of drug. However, this section refers to an amount between 0.05 ng and 500 mg (a huge range) *"of drug, carrier, fills, excipients, etc. with individual devices containing for example, 25 ng, 1 mg, 5 mg, 125 mg, 250 mg, 500 mg, and the like"*. This is not the same as disclosing a discrete amount of active agent which is released sublingually of between one and fifty milligrams.

Barclay not only does not disclose the claimed drugs, but the examiner makes no correlation between the drugs that are disclosed (the examiner refers to prochlorperazine, nitroglycerin, etc on page 5 of the office action) and the claimed drugs. All of the drugs Barclay describes, such as prochlorperazine and nitroglycerine, are for immediate release and uptake.

Barclay also does not disclose the use of a sustained release or chewable formulation which is swallowed, nor does he lead one of skill in the art to substitute such formulations for those that he does describe. Barclay describes an osmotic device. Indeed, Barclay teaches away from either a sustained release or a chewable second portion. The one embodiment with an HPMC coating might delay release of the second component but would not result in sustained release. Chewing would destroy an osmotic device.

Barclay describes a device that is designed to deliver the same drug into the oral cavity and, optionally, into the GI tract – the device has only one drug reservoir (see Fig. 1, 2, 3, 4 and col. 8, lines 31-35). This device cannot be used to deliver two different drugs as described by Hirsh et al. and, therefore, distinctively different.

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Barclay's device is "designed to be retained in the mouth for periods on the order of about 0.5 to 12 hours" (col. 7, lines 35-36). Hirsh describes a composition wherein the first component [that contains drug to be absorbed in the mouth into the systemic circulation] "disintegrates or dissolves within 10 minutes, when composition is contacted with saliva" (the examiner's comment that appellants have no such claim is in error - the attention of the Board is directed to Claim 48). Barclay indeed discloses a variety of drugs that can be delivered using the device (col. 10, line 50 to col. 11, line 35), however, only one drug can be delivered using Barclay's device (see above). The drug could be either one intended for absorption within the oral cavity (e.g. nitroglycerine) or drug intended for absorption within the GI tract (e.g. prochlorperazine). Applicants' composition allows for administration of drug intended for absorption within the oral cavity followed by drug intended for absorption within the GI tract.

Applicants select and use the drugs for delivery within the oral cavity based on their ability to be absorbed through the oral mucosa membrane. Barclay makes no distinction between two different classes of drugs: (a) drugs that are released within the oral cavity and absorbed within the oral cavity and (b) drugs that are released within the oral cavity, then swallowed with saliva, and finally absorbed in the GI tract. Applicants have designed a composition that can deliver drugs from both classes in a single dosage form.

The examiner's argument that limitations such as "chewable" and for "sublingual" versus for "buccal" delivery are not meaningful, but merely intended use limitations. This is mere semantics. Those skilled in the art know the difference between a formulation that is chewable and one that is not. For example, an enteric coated tablet

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is not considered "chewable" since the coating is intended to protect passage of the drug through the stomach – chewing it first would remove the protective coating.

Formulations for sublingual delivery versus buccal delivery must be shaped and formed of a material that will fit under the tongue and dissolve rapidly, as well as contain a drug that can be safely and effectively delivered into the blood stream by absorption at a site underneath the tongue. These are not mere "intended use" limitations; they are limitations those skilled in the art would understand are critical as to the selection of the drug and dosage and carrier.

Accordingly, nothing in Barclay would lead one skilled in the art to the subject matter of claims 33, 41 and 55, and claims dependent thereon.

3. *Rejection of claims 33-43, 45, and 47-57 as obvious under 35 U.S.C. 103 over U.S. Patent No. 5,702,723 to Griffin in view of U.S. Patent No. 4,661,492 to Lewis, et al.*

Griffin

Griffin teaches "a multi-stage delivery system in the form of a pill having an outer layer comprising an active substance or substance that will dissolve and have a beneficial effect somewhere in the mouth or upper respiratory area with the subsequent layers dissolving and the contained substances acting deeper within the body such as in the gastro-intestinal area or systemically" (col. 3, lines 8-13).

Griffin emphasizes the fact that "saliva-soluble" active ingredient of an external layer is "locally acting agent providing a condition-related therapeutic effect in the mouth, esophagus or bronchial tract" (col. 6, lines 33-35). The active ingredient of an internal layer is "internally or systemically active" (col. 6, lines 23-24). Both active

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ingredients of Applicants' composition are systemically acting agents that are absorbed into the bloodstream at the different sites of the human body: first ingredient within the oral cavity and the second ingredient within the GI tract.

As the Examiner notes, Griffin describes drugs in a coating of HPMC, which would delay release (see Griffin, col. 4, lines 5-23), with an outer coating of a substance that dissolves rapid and tastes good (col. 3, lines 24-25). "The outer coating can include calcium carbonate". This does not teach a coating that is dissolved and absorbed sublingually. Indeed, as noted in the article submitted with the last response, the ability of a drug to be absorbed sublingually depends on its ionization state that is controlled by pH. It is as likely that calcium carbonate would prevent sublingual absorption of many of the disclosed drugs as it is that it would allow sublingual absorption, absent a teaching that the pH must be adjusted appropriately!

There is no disclosure of the claimed dosage. The only dosage referenced is at col. 3, lines 46-47, which refers to administration of 325 or 405 mg of aspirin – significantly more than the claims one to fifty for sublingual delivery from the first component, as claimed.

There is no disclosure of the time periods for delayed release from the second component as defined by the dependent claims.

Lewis

Lewis merely discloses a particular combination of naltrexone with buprenorphine for parenteral or sublingual delivery. Lewis does not describe a first component which *must* be delivered sublingually and a second which *must be* swallowed, for sustained release, or chewed and swallowed.

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As the examiner correctly pointed out, Lewis requires 0.1 to 0.4 mg; appellants claim the use of between one and fifty mg.

There is no teaching that would lead one to substitute the drugs of Lewis for the drugs of Griffin, nor even if they did, would the resulting combination lead to the claimed drug formulation, much less with any reasonable expectation of success. Accordingly, Griffin in combination with Lewis does not make obvious the subject matter of claims 33-43, 45, and 47-57.

4. *Rejection of claims 44 and 46 as obvious under 35 U.S.C. 103 over U.S. Patent No. 5,702,723 in view of U.S. Patent No. 4,814,181 to Jordan, et al.*

Griffin is discussed above.

Jordan

With respect to claims 44 and 46, Jordan does not make up for the deficiencies of Griffin. Claim 44 requires that the first component be within an effervescent coating that releases drug instantly sublingually. Claim 46 requires a first component formulated for sublingual release in combination with either a chewable or sustained release second component, further including a delayed release coating. Griffin does not lead one skilled in the art to make a formulation containing a first drug that must be delivered sublingually, in combination with an effervescent coating. Indeed, Jordan is such a specialized device, and so different from what is claimed, it is impossible to see how or why anyone would be led to combine any of its disclosure with that of Griffin. The device of Jordan is an *osmotic* device, like that of Barclay. There is nothing that would provide for an immediate release of the first component, much less in an effervescent form. Accordingly, claim 44 is not obvious from Griffin and Jordan.

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Claim 46 is also not obvious. As discussed above, Griffin does not make obvious claim 33. Therefore, claim 46, which recites that the device incorporates a delayed release coating, does not make up for the deficiencies of Griffin and claim 46 is not obvious over the combination of Griffin and Jordan.

In summary, Jordan does not teach two formulations which deliver in different locations, one sublingually, and one after the remaining device is swallowed, where the second device, not the first, is coated so that delayed release occurs within a defined time period.

5. *Rejection of claims 33-39, 42-50, 52, 53, and 55-57 as obvious under 35 U.S.C. 103 over GB 800,973 to Sterling in view of U.S. Patent No. 4,661,492 to Lewis, et al.*

The rejection of claim 33 is stated to be due to appellants' removal of the limitation of "the ingredient having a molecular weight not exceeding 350 Daltons". This makes no sense, since the claim was actually narrowed to define a composition containing only the recited compounds (Buprenorphine, Parecoxib, Aceclofenac, Buspirone, Ipsapirone, Fexofenadine, Loratadine, Dexbrompheniramine, Temelastine, Verapamil, Amlodipine, Ergotamine Tartrate, Dihydroergotamine, Ondansetron, Prochlorperazine, Sildenafil, Alprostadil, Sufentanil, Lofentanil, Carfentanil, Nalbuphine, Droperidol, and Haloperidol) in a dosage of between one and fifty milligrams in the first component. None of the named drugs in the defined dosage are described in either GB 800,973 or Lewis.

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GB 800,973 Sterling

GB 800 863 describes a two component drug delivery device. There is no disclosure of anything resembling an immediate release, effervescent coating containing the first agent to be released.

Leslie is discussed above. U.S. Patent No. 4,322,433 to Leslie fails to make up for the deficiencies of GB 800,973. Leslie does not disclose the claimed drug dosage. Sterling does not disclose the claimed drug dosage. Leslie leads one skilled in the art to formulations containing drug such as nitroglycerine which readily dissolves in the absence of any coatings or additives, for *delivery to the skin, i.e., percutaneous delivery (see abstract)*.

GB 800 973 also fails to describe a second component which is either chewable or provides sustained release. Leslie also fails to make up for this deficiency, nor would either lead one skilled in the art to make such a modification to what is disclosed in GB 800 973, as claimed. GB 800 973 discloses only immediate release formulations, and emphasizes the need for rapid release, thereby teaching away from a sustained release formulation. Leslie describes formulations containing lipophilic carriers for transdermal or percutaneous delivery. Although these may provide sustained release, one skilled in the art would never combine a transdermal formulation with an oral formulation. According, claims 33 and 55, and claims dependent thereon, are not obvious from GB 800 973 alone or in combination with Leslie.

6. *Summary*

The claims recite either that the two component formulation has a chewable or sustained release second component for oral ingestion following immediate release

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sublingually of a first component (claims 33 and 55, and claims dependent thereon) or an effervescent first component which is released and absorbed sublingually (claim 44, and claims dependent thereon).

Sublingual release and absorption is quite different from other types of oral delivery. An article from the internet which provides a concise explanation of sublingual absorption and the mechanics thereof was enclosed with the last response. A number of factors are critical to the amount of absorption. *The examiner has apparently not taken into consideration either document provided with the last response to show why those skilled in the art would not reach the conclusions that were used as the basis for the rejection.*

The standard under 35 U.S.C. 103 for obviousness is quite clear: not only must the references disclose each claimed feature, but the motivation to combine as applicants have done, with a reasonable expectation of success. The motivation must come from the references themselves, not merely an assertion that such a combination would be obvious.

None of the prior art discloses or leads one of ordinary skill in the art to a drug formulation which contains (1) a component which is rapidly released in the mouth, has a low molecular weight under 350 daltons or is one of the listed drugs, present in a dosage between 1 microgram and 50 mg, which is absorbed sublingually, in combination with (2) an inner second component which is released after swallowing. The prior art does not teach the selection of an agent for sublingual administration, which is rapidly released and absorbed. Accordingly, the prior art neither discloses nor makes obvious the claimed subject matter.

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(9) SUMMARY AND CONCLUSION

The claims are definite as required under 35 U.S.C. 112, second paragraph. The claims are neither disclosed by nor obvious over the cited art, alone or in combination.

For the foregoing reasons, Appellants submit that the claims 33-57 are patentable.

Respectfully submitted,



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Appendix: Claims On Appeal

33. (previously presented) A pharmaceutical composition comprising:

(a) a first intraoral portion which rapidly dissolves or disintegrates intraorally to release a therapeutically effective amount of at least one pharmaceutically active ingredient which is absorbed sublingually in a therapeutically effective level, the active ingredient selected from the group consisting of Buprenorphine, Parecoxib, Aceclofenac, Buspirone, Ipsapirone, Fexofenadine, Loratadine, Dexbrompheniramine, Temelastine, Verapamil, Amlodipine, Ergotamine Tartrate, Dihydroergotamine, Ondansetron, Prochlorperazine, Sildenafil, Alprostadil, Sufentanil, Lofentanil, Carfentanil, Nalbuphine, Droperidol, and Haloperidol, being present in an amount between 1 micrograms and 50 mg, and having a rapid onset following intraoral administration; and

(b) a second oral portion located within the first portion which is released into the gastrointestinal tract in a therapeutically effective amount after the intraoral portion has disintegrated or dissolved, wherein the second portion is either a sustained release or chewable formulation.

34. (previously presented) The pharmaceutical composition of claim 33 wherein the active ingredient of the intraoral component undergoes first pass metabolism.

35. (Original) The pharmaceutical composition of claim 33 in a tablet or capsule unit dosage form.

36. (Original) The pharmaceutical composition of claim 35 wherein the unit dosage form is a tablet and the second oral portion of the composition is an inner core of the tablet surrounded by an outer coating of the first intraoral component.

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37. (Original) The pharmaceutical composition of claim 35 wherein the unit dosage form is a multi-layer tablet wherein the second oral portion of the composition comprises one or more inner layers of the tablet and the first intraoral component comprises one or more of the outer layers of the multi-layer tablet.

38. (Original) The pharmaceutical composition of claim 36 wherein the outer coating is a film coat that is applied as a layer to the inner core.

39. (Original) The pharmaceutical composition of claim 36 wherein the outer coating is a compression coat that is compressed around the inner core.

40. (Original) The pharmaceutical composition of claim 33 comprising an outer film coating comprising at least one pharmaceutically acceptable coating polymer selected from the group consisting of cellulose, hydroxypropyl methylcellulose, methylcellulose, polyvinylpyrrolidone, and polyethylene glycol, a pharmaceutically acceptable plasticizer, a pharmaceutically acceptable glidant and a pharmaceutically acceptable colorant.

41. (previously presented) A pharmaceutical composition comprising:
(a) a first intraoral portion which rapidly dissolves or disintegrates intraorally to release a therapeutically effective amount of at least one pharmaceutically active ingredient which is absorbed sublingually in a therapeutically effective level,

the active ingredient having a molecular weight not exceeding 350 daltons or an active ingredient selected from the group consisting of Buprenorphine, Parecoxib, Aceclofenac, Buspirone, Ipsapirone, Fexofenadine, Loratadine, Dexbrompheniramine, Temelastine, Verapamil, Amlodipine, Ergotamine Tartrate, Dihydroergotamine, Ondansetron, Prochlorperazine, Sildenafil, Alprostadil, Sufentanil, Lofentanil,

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Carfentanil, Nalbuphine, Droperidol, and Haloperidol, being present in an amount between 1 micrograms and 50 mg, and having a rapid onset following intraoral administration, and

the first intraoral portion comprising a pharmaceutically acceptable effervescent agent which generates effervescence when contacted with salivary fluid; and

(b) a second oral portion located within the first portion which is released into the gastrointestinal tract in a therapeutically effective amount after the intraoral portion has disintegrated or dissolved.

42. (Original) The pharmaceutical composition of claim 33 comprising a pharmaceutically acceptable flavoring agent in the first intraoral component.

43. (Original) The pharmaceutical composition of claim 33 wherein the second oral component is in a sustained release formulation.

44. (Original) The pharmaceutical composition of claim 43 wherein the sustained release is over a period of 0.5 to 24 hours.

45. (Original) The pharmaceutical composition of claim 33 comprising a delayed release coating.

46. (Original) The pharmaceutical composition of claim 45 wherein release is delayed for a period of 0.5 to 12 hours.

47. (Original) The pharmaceutical composition of claim 33 wherein the second oral component is chewable and comprises at least one pharmaceutically acceptable excipient suitable for a chewable medication and a flavoring agent.

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48. (Original) The pharmaceutical composition of claim 33 wherein the first intraoral component disintegrates or dissolves within 10 minutes, when the composition is contacted with saliva during intraoral administration.

49. (Original) The pharmaceutical composition of claim 33 wherein the second oral component remains intact until the intraoral administration of the first intraoral component has been delivered.

50. (Original) The pharmaceutical composition of claim 33 further comprising a pharmaceutically acceptable signaling system located between the first intraoral component and the second oral component that is detectable by the patient upon substantial release of the pharmaceutically active ingredient in the first intraoral component.

51. (previously presented) The pharmaceutical composition of claim 41 wherein the pharmaceutically active ingredient in the first intraoral component having a molecular weight not exceeding 350 Daltons is selected from the group consisting of analgesics, antihistamines, antidiarrheals, anxiolytics, hypnotics, stimulants, cardiovascular drugs, pulmonary drugs, anti-hypertensives, anti-emetics, anti-inflammatory drugs, renal drugs, steroids, drugs for neurological disorders, anti-psychotic drugs, drugs for treating endocrine disorders, drugs for promoting immune response, drugs for treating osteoarthritis, drugs for treating glaucoma, drugs for treating allergic rhinitis, drugs for treating anemias and other hematological disorders, drugs for treating infectious diseases, drugs for the treatment and symptoms of cancer, drugs for insomnia, and antidiabetic drugs.

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52. (Original) The pharmaceutical composition of claim 33 wherein the active ingredient in the first intraoral composition has a lower bioavailability upon oral administration when compared to intravenous administration.

53. (Original) The pharmaceutical composition of claim 33 wherein the active ingredient in the first intraoral composition is in a dosage of between 10 micrograms and 30 mg.

54. (previously presented) The pharmaceutical composition of claim 41 wherein the active ingredient has a molecular weight of less than 350 Daltons.

55. (previously presented) A process for the preparation of a pharmaceutical composition in unit dosage

(a) a first intraoral portion which rapidly dissolves or disintegrates intraorally to release a therapeutically effective amount of at least one pharmaceutically active ingredient which is absorbed sublingually in a therapeutically effective level,

the active ingredient selected from the group consisting of Buprenorphine, Parecoxib, Aceclofenac, Buspirone, Ipsapirone, Fexofenadine, Loratadine, Dexbrompheniramine, Temelastine, Verapamil, Amlodipine, Ergotamine Tartrate, Dihydroergotamine, Ondansetron, Prochlorperazine, Sildenafil, Alprostadil, Sufentanil, Lofentanil, Carfentanil, Nalbuphine, Droperidol, and Haloperidol, being present in an amount between 1 micrograms and 50 mg, and having a rapid onset following intraoral administration; and

(b) a second oral portion located within the first portion which is released into the gastrointestinal tract in a therapeutically effective amount after the intraoral portion has disintegrated or dissolved,

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which comprises the steps of:

(i) providing the second oral component as an inner tablet core or as at least one layer of a multi-layer tablet core or as an uncoated capsule, wherein the second oral component is either a sustained release or chewable formulation; and

(ii) applying the first intraoral component as an outer layer or as several outer layers forming an outer coating on the first portion.

56. (Original) The process of claim 55 wherein the active ingredient exhibits first pass metabolism.

57. (Original) The process of claim 55 wherein the active ingredient has a molecular weight of less than 350 daltons.

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Appendix I: Claims On Appeal

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Applicant: Jane C. Hirsh, Kamal K. Midha, and Whe-Yong Lo

Serial No.: 09,858,016

Art Unit: 1616

Filed: May 15, 2001

Examiner: Sharmilas Gollamudi

For: *PHARMACEUTICAL COMPOSITION FOR BOTH INTRAORAL AND
ORAL ADMINISTRATION*

(45051403.1)

OCT 13 2004

PTO/SB/21 (09-04)

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TRANSMITTAL FORM (to be used for all correspondence after initial filing)	Application Number	09/858,016
	Filing Date	May 15, 2001
	First Named Inventor	Jane C. Hirsh
	Art Unit	1618
	Examiner Name	Shamllas Gollamudi
Total Number of Pages in This Submission	Attorney Docket Number	CP 102

ENCLOSURES (Check all that apply)		
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Application Number	09/858,016
Filing Date	May 15, 2001
First Named Inventor	Jane C. Hirsh
Examiner Name	Sharmilas S. Gollamudi
Art Unit	1616
Attorney Docket No.	CP 102

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1202 18	2202 9	Claims in excess of 20	
1201 88	2201 44	Independent claims in excess of 3	
1203 300	2203 150	Multiple dependent claim, if not paid	
1204 88	2204 44	** Reissue independent claims over original patent	
1205 18	2205 9	** Reissue claims in excess of 20 and over original patent	

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1052 50	2052 25	Surcharge - late provisional filing fee or cover sheet	
1053 130	2053 130	Non-English specification	
1812 2,520	1812 2,520	For filing a request for ex parte reexamination	
1804 920*	1804 920*	Requesting publication of SIR prior to Examiner action	
1805 1,840*	1805 1,840*	Requesting publication of SIR after Examiner action	
1251 110	2251 55	Extension for reply within first month	
1252 430	2252 215	Extension for reply within second month	
1253 980	2253 490	Extension for reply within third month	
1254 1,530	2254 765	Extension for reply within fourth month	
1255 2,080	2255 1,040	Extension for reply within fifth month	
1401 340	2401 170	Notice of Appeal	
1402 340	2402 170	Filing a brief in support of an appeal	
1403 300	2403 150	Request for oral hearing	
1451 1,510	1451 1,510	Petition to Institute a public use proceeding	
1452 110	2452 55	Petition to revive - unavoidable	
1453 1,330	2453 665	Petition to revive - unintentional	
1501 1,370	2501 685	Utility issue fee (or reissue)	
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1808 180	1808 180	Submission of Information Disclosure Stmt	
8021 40	8021 40	Recording each patent assignment per property (times number of properties)	
1809 790	2809 395	Filing a submission after final rejection (37 CFR 1.129(a))	
1810 790	2810 395	For each additional invention to be examined (37 CFR 1.129(b))	
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